EXHIBIT 3

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increased IL15.
Q. Doctor, from the time you wrote this paper in 2016 -- actually, you submitted at the end of 2015, published in 2016?
A. Uh-hum.
Q. -- correct me if I'm wrong, but there's been no published literature reporting on experiments of any possible mechanism that would explain olmesartan-associated enteropathy; correct?
MR. SLATER: Objection.
You can answer.
THE WITNESS: I don't know when the Marietta paper was published, but --
BY MR. PARKER:
Q. You cite it here, so it had to be published before you wrote this paper, reference number 7.
A. Okay. Having studied it more in the months or even year since this was published, I think that Marietta

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puts forth a plausible mechanism.
Q. Plausible. Is there any other basic science -- strike that.
Is there any other publication reporting on experiments of any type that describes a mechanism that has -- that was published after this paper (Indicating) was published?
A. I'd have to think about that for a minute.
Q. Take a few seconds to think about it.
A. Okay.
(Pause.)
THE WITNESS: There's also the Scialom paper in PLoS One. I suppose I did reference that, though, as well.
MR. PARKER: That's reference 8 in your paper.
THE WITNESS: There may have been other studies where they did immunophenotyping of the inflammatory cells in this

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condition. I'm not remembering them offhand.
BY MR. PARKER:
Q. Or if there are any.
A. I'm not remembering if there are any.
Q. Okay.
And so the record's clear, you have the advantage of looking at your notebook prepared for you by counsel with all of your papers originally referenced and supplemented; correct?
A. I do have that, yes.
Q. Okay.
(Pause.)
THE WITNESS: So I don't think that there have been additional basic science studies on this topic, but I think there have been additional clinical observations that have added to our understanding of the mechanism of illness.
Some of the -- there's been

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work reporting the HLA-DQ2/DQ8 prevalence in olmesartan enteropathy which has -- additional reports of such have come out over the last couple of years since the majority of this paper was written and which support the idea that this is an immune-mediated process.
And I do believe other authors have found ANA, antinuclear antibodies, which again support an immune pathogenesis. And I believe there have been other studies doing CD8 staining of biopsies, which I think would also point to a T cell response.
BY MR. PARKER:
Q. You tell me when you're done, Doctor. I don't want to --
A. Okay.
Q. "Okay," you're done?
A. Yeah, I'm done.

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Q. Okay. Doctor, that notebook, does it contain any papers that are not referenced in your report or on the supplemental list?
A. Yes.
MR. PARKER: Then I'm going to need to get a copy of the index only. We can mark that as an exhibit or --
MR. SLATER: The index of what?
MR. PARKER: Of his notebook.
MR. SLATER: You can get a copy of it.
MR. PARKER: Okay. Yeah.
THE WITNESS: Now or --
MR. SLATER: No.
MR. PARKER: No. We'll wait until later, but --
MR. SLATER: I can even have it e-mailed to you. Whatever you want, I don't care.
MR. PARKER: I just need the

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index of that, a copy of it.
BY MR. PARKER:
Q. Doctor, let's turn to the discussion of epidemiological studies on 131 of your report.
A. Sure -- of my paper.
Q. I'm sorry. Yes. Thank you. I'm sorry.
A. Sure.
Q. And here you're -- in the context of your systematic review with the emphasis on histopathology, you discuss epidemiological studies; correct?
A. Correct.
Q. And the two that you mentioned are the Basson paper and the Greywoode paper down at Columbia, the institution at which you work.
A. Okay. Let me read through that.
Q. Sure.
A. I do discuss Basson, Greywoode, yes.
Q. Okay.

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When you wrote this paper, were you aware of the Padwal paper that was published in 2014?
A. I don't believe I was.
Q. Was there a literature search done by you or others in this group to collect the relevant literature for this systematic review?
A. Uh-hum.
Q. And who conducted the search with respect to epidemiology, if you recall?
A. I can't say that I do recall.
Q. Were you personally aware of the data contained in the Manhaller letter following the Mayo Clinic report?
A. I am familiar with that.
Q. Were you familiar when you wrote this paper in 2016?
A. I don't believe so.
Q. Were you familiar with -- excuse me. Had you read either of the two Mini-Sentinel reports published by or

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released by the FDA in 2016 when you read this report? And let me rephrase that question, because it could be interpreted to be incorrect.
A. Okay.
Q. In 2016 when you wrote this report, had you read either of the two Mini-Sentinel reports looking at olmesartan and other ARBs and celiac disease?
A. I don't know -- I don't know if I had read the Mini-Sentinel. I definitely read the FDA statement but I --
Q. I'm asking about --
A. I don't recall if I read that.
Q. -- their data. Okay.
So right now, you're not able to tell me whether or not when you wrote the systematic review you personally were aware of those other three pieces of data.
A. I believe I was not.

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MR. PARKER: Okay. Let's put this paper aside and go on to an abstract you published.
THE WITNESS: Okay.
- - -
(Deposition Exhibit No. Lagana-11, Abstract 757 "Angiotensin Receptor Blockers Other Than Olmesartan Are Not Associated with Histologic Evidence of Duodenitis" by Lagana, et al, was marked for identification.)
- - -
BY MR. PARKER:
Q. Exhibit No. 11 is an abstract in which you were the lead author, abstract number 757?
A. Uh-hum.
Q. And I don't see on this paper -- can -- do you remember the year in which this was submitted at that professional meeting?
A. Maybe I can figure it out

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based on the paper, the subsequent paper.
Q. Maybe I can make it easier for you. Would this have been released before your paper was published in 2015 of your study of the 20 olmesartan users and 20 controls and so on?
A. Yes, it would be before that.
Q. So sometime before that paper was published in 2015, you presented this abstract at a medical conference; is that right?
A. Yep.
Q. Okay.
Now, fair to say that at the time of this conference, you had already concluded that olmesartan was causing enteropathy in the general population?
A. When you say general population, what -- I mean, in specific patients, is that --
Q. No. I mean -- well, you tell me. Had you reached a conclusion on general causation at the time you

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published this abstract?
MR. SLATER: Didn't you just say general population?
MR. PARKER: I did say general population and the witness asked me a question. I said, had you reached an opinion on general causation at the time you published this abstract.
THE WITNESS: I don't recall.
BY MR. PARKER:
Q. Had you reached a conclusion that in some discrete patients, olmesartan was causing enteropathy?
A. I believe I probably had reached that conclusion.
Q. Nevertheless, this abstract reports on your -- you and others' -- review of biopsies of non-olmesartan ARB users compared to age and sex matched controls to determine if there was any difference in various histopathologic occurrences.

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A. Uh-hum.
Q. That's a yes?
A. Oh, yes. Yes.
Q. Okay.
What drove you to do this study?
A. There are really two questions that we were attempting to answer with this study and the subsequent publication; and those questions were, one, do other -- is there evidence that other ARBs have similar effects and, two, is there a spectrum of histologic findings -- or let me rephrase that -- can we find similar histologic findings in patients without a severe syndrome of diarrhea and weight loss who are taking olmesartan.
So this data that we presented in this abstract only related to the first part of that question, which is, do non-olmesartan ARB users have any histologic abnormalities.
Q. But are you telling me these

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ten ARB users had not developed symptoms of diarrhea?
A. They did not have diarrhea.
Q. What clinical symptoms did they have?
A. These patients had abdominal pain.
Q. Okay.
And that's it?
A. Yes.
Q. So they came into Columbia with complaints of abdominal pain, biopsies were taken, and you went back in this study and reviewed various histopathologic findings in those patients and controls.
A. Correct.
Q. And the controls, as I mentioned, or as you mention, are age and sex matched people.
A. Uh-hum.
Q. Why were they being seen at Columbia?
A. Also for abdominal pain.

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Q. There's no -- was there any attempt to control for other confounders such as drug use? I don't mean illicit --
A. Yeah, other drugs?
Q. Other drugs.
A. No, no.
Q. So you don't know whether -- how many of the ARB users, if any, and the controls were using drugs known to cause diarrhea or, conversely, to prevent diarrhea.
A. I don't know that.
Q. And nonetheless, in this study, you concluded that there was no difference in the occurrences of these various histopathologic findings between the non-olmesartan ARB users and controls.
A. Correct.
Q. How did these various outcomes -- how were they selected -- excuse me. Let me rephrase the question.
Why were these particular

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ones selected?
A. These are sprue-like findings, so findings that would be analogous to what we might see in celiac disease or olmesartan enteropathy.
MR. PARKER: Now, I want to now turn to the 2015 paper. You can keep that abstract. We may need it.
THE WITNESS: Okay.
- - -
(Deposition Exhibit No. Lagana-12, 2015 Article "Sprue-like histology in patients with abdominal pain taking olmesartan compared with other angiotensin receptor blockers" by Lagana, et al, was marked for identification.)
- - -
BY MR. PARKER:
Q. And Exhibit 12 is your paper that we alluded to earlier that was published in 2015?

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A. 2014 -- or, yeah, yeah, 2015, published online in 2014.
Q. And was the idea for this paper or this study generated after you presented your abstract that we just got done discussing?
A. No. These are part of the same project.
Q. Had you started this project which became this published paper, Exhibit 12, at the time you presented the abstract at the scientific meeting?
A. Yes. This -- the abstract that was presented to the meeting was preliminary data from this study.
Q. So are 10 of the ARB users reflected in -- in and among the 20 that are profiled in this paper?
A. Yes.
Q. And are the ten profiled in the matched controls in this paper?
A. Yes.
Q. And are the matched controls in the abstract -- do they appear -- as

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we looked at this column, are they the matched controls to ARB users or to olmesartan users?
A. You're talking about table 2?
Q. Yes, sir.
A. The controls in this abstract would be part of the 20 controls that are in the right-hand side here, matched controls, to other ARB users.
Q. And is there any difference in the two variables on which you matched, age and sex, between the matched controls for olmesartan and the matched controls for ARB users?
A. Are there any difference -- well --
Q. Essentially, is that a homogeneous group?
A. Right. So the question would really be, are the olmesartan users the same as the other ARB users in this study --
Q. No --

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A. -- because the controls are matched to -- the controls are matched to the olmesartan users or to the ARB -- other ARB users.
Q. But my question is, is there any difference in the age and sex profile of the matched controls for olmesartan compared to the matched controls for ARB users?
In other words, Doctor, look at table 1 and do you see any material difference in the patient characteristics of the matched controls for olmesartan compared to the matched controls for ARB users?
A. Well, there are more women in the olmesartan group than the ARB group.
Q. And is that a material difference with regard to the issues you're looking at in this paper?
A. I don't know. I didn't study that. It could be.
Q. Doctor, did you -- well, let

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me rephrase the question. There was no effort to control in this study for drug use.
A. For other drugs.
Q. Other drug use.
A. Not to my recollection.
Q. So you have no idea as we sit here today how many of the olmesartan users, ARB users, or the controls for either one were taking other drugs known to cause or prevent diarrhea, for example.
A. That's correct.
Q. So the study was done and -- strike that. Let me ask the question, do you have a protocol for this study?
A. A protocol like --
Q. Did you develop a protocol for this study?
A. Did I develop a protocol --
Q. Well, let me back up. I don't mean to be facetious. You understand what I'm asking when I say was there a written protocol created for the

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study?
A. Yes, I believe there was.
Q. So you believe that you or others in your group wrote up how this study was to be conducted, what the primary endpoints were going to be, and what the statistical analysis was going to be.
A. Uh-hum.
Q. That would be yes?
A. Oh, yes.
Q. Okay.
And do you still have that?
A. I don't know. Possibly.
Q. And possibly where would it be amongst your papers?
A. If I have it, it would be in my office.
Q. Did you have to get institutional review board approval for this study?
A. I believe we did.
Q. So if you had a protocol, it would had to have been submitted to the

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Columbia IRB?
A. Uh-hum.
Q. Is that right?
A. I believe so.
Q. Now --
A. Which I believe we did.
Does it say here?
Q. I frankly don't remember that aspect of what you assert you did or not.
A. This study was approved by the Columbia University Medical Center's institutional review board.
Q. And this was a retrospective study, was it not?
A. It was.
Q. Now, Doctor, before you undertook the study, did you ask a biostatistician to determine what the size of this study would have to be in order to find, if it existed, a statistically significant difference between the various groups studied?
A. I wish I did. No.

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Q. Did anyone -- I mean, you've got some pretty senior people here, Peter Green. Did a discussion ever come up, well, before we launch into this, let's figure out how many files we actually have to look at so if there's something real there, we can report a statistically significant difference?
A. I do believe I discussed that with Dr. Lebwohl and I think that we came up with a number of 20 in each group, and I think that was sort of a best estimate. We didn't run pretest statistical testing to come up with that number. We kind of used a gestalt approach.
Q. A couple times today and in your 2016 paper, you comment that some of the epidemiological studies that have failed to find an association were underpowered, I think is your word; is that right?
A. Yep.
Q. So you are understanding of

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the need to power studies so that they are capable of achieving a statistically significant result?
A. Yes.
Q. And I'm not understanding why that exercise was not done here.
MR. SLATER: Objection.
You can answer.
THE WITNESS: Well, I wish we had. We didn't. I don't recall a specific reason why.
MR. PARKER: Okay.
BY MR. PARKER:
Q. It wasn't that if we don't get positive results, we will be able to say that it wasn't powered enough.
A. That was not my thinking.
Q. Okay. I just had to ask, Doctor.
MR. SLATER: You didn't have to, but you wanted to.
MR. PARKER: Well, I wanted to and I had to.
MR. SLATER: You didn't have

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to.
BY MR. PARKER:
Q. So, Doctor, let's take a look at what happened here. When you did this study, you looked at -- and is it correct to say that everything down to increased crypt apoptosis on table number 2 were the primary outcomes of your study?
A. Correct.
Q. And so when you did the study and you looked at whether you found these described conditions in the olmesartan users, the matched controls, the other ARB users and the matched controls, you found that your study had failed to find a statistically significant difference in any of these six or seven outcomes either in the olmesartan users or the other ARB users; correct?
A. Yep.
Q. And then with negative results, you said, well, let's go back

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and now let's do a composite outcome and see if we come up with something if we do that. Right?
A. We examined -- we did a post hoc analysis of a composite outcome, yes.
Q. And -- but a -- just so the record's clear, a composite outcome was not one of your primary outcomes.
A. Right.
Q. And is the composite outcome what's described here on table 2 as architectural abnormalities, generalized increased IEL, and chronic inflammation?
A. Uh-hum. Yep.
Q. Yes? Okay.
A. Oh, yes. Yes.
Q. Please tell us, sir, what is included in the phrase "architectural abnormalities"?
A. Villous atrophy and crypt hyperplasia.
Q. What is included in the phrase "generalized increased IEL"?
A. Generalized IEL increase.

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Q. So the --
A. Individual variable number 4, the fourth one down.
Q. I see. And, lastly, chronic inflammation.
A. The fifth one down.
Q. So essentially what you did is, you combined all of the top individual endpoints into a composite, but it seems that you left out eosinophilia and neutrophilia. Am I correct?
A. We left those out. We also left out increased crypt apoptosis. We chose the ones that are most common in celiac disease.
Q. So if I had a GI expert in celiac disease, he would say, I agree that eosinophilia, neutrophilia, and increased crypt apoptosis are not common features of celiac disease?
A. He would -- he or she would agree that they're less significant findings or less robust findings in

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celiac disease.
Q. Explain to me your thinking as to why in creating a composite endpoint you chose to exclude some that previously were considered to be features of celiac disease.
MR. SLATER: Objection.
You can answer.
THE WITNESS: I'm going to have to ask you to clarify that.
MR. PARKER: Sure.
THE WITNESS: What do you --
BY MR. PARKER:
Q. You said to me earlier that you came -- and I say "you," I mean your group -- identified these individual characteristics because you said they were features of celiac disease.
A. Uh-hum.
Q. Right? That would be a yes?
A. Yes, yes.
Q. Okay.
A. The most common, most prominent, features of celiac disease.

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Q. Very well. And then when the study failed to find a positive result -- a statistically significant positive result -- you went back and combined some number of those features, but not all of them. Right?
A. I understand. Yeah, so some of these features that we looked for are not really classically associated with celiac disease, such as neutrophils, what I refer to as neutrophilia, so these -- just give me a second to explain myself properly.
Q. Sure, please, take your time.
A. We looked at the cardinal features of celiac disease and then added a couple of occasionally present features or minor players in the pathogenesis of celiac disease, such as eosinophils and neutrophils, as well as crypt apoptosis, which is kind of an interest of mine, but is not something that people generally describe as a vital part of the

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histopathology of celiac disease.
So when we -- we looked at all these individual features and, as you say, we did not find any statistically significant difference.
And I'll point out that not every study that you do is going to get you a Nobel Prize and I didn't expect one from this one.
But then we looked at a composite outcome of the most common celiac disease-related findings and what we found there was that there was a trend towards significance, point one, that the olmesartan users had more of these -- had -- when you look at the composite outcome, there's more -- more positive findings in the olmesartan users than the matched controls, and that result approached but didn't reach statistical significance.
Q. And there was essentially no difference between the olmesartan group and the other ARB groups.

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MR. SLATER: Objection.
You can answer.
MR. PARKER: Ten versus nine.
THE WITNESS: In the composite outcome, there was essentially no difference.
BY MR. PARKER:
Q. And that's what we're talking about, because you don't claim that there was any trending with any of the individual endpoints, do you?
A. I don't remember making that point.
Q. Well, my question is -- my question is confirming that you never made the argument that there was a trend for any of the primary endpoints. The trend that you describe is only in connection with the composite post hoc endpoint.
A. Okay. And I'm going to have to pause there because there was a trend towards an increased mean maximum IEL

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count compared to the matched controls. There, the P value is .09. Let me see if we -- I don't recall if I made a statement to that effect. But I'll -- I'll look at that now.
Q. Sure.
(Pause.)
THE WITNESS: On the results -- in the results section on the top of the right-hand side of page 30, we report, without really a value judgment one way or the other, saying that the mean maximum IEL count was 13.7 in the olmesartan group compared to 10 -- with 10.6 for controls, open parentheses, P equals .09.
So that is a trend.
BY MR. PARKER:
Q. My question, however, is, you make an assertion in this paper that there was a trend in certain outcomes. You attribute that statement of a trend to the composite outcome. Am I correct?

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A. Well, we put in verbiage about a trend with regard to the composite outcome. We give the data that demonstrates a trend with both the composite outcome and the mean IEL count.
Q. Let's look at the mean IEL count. There's essentially no difference between olmesartan and other ARB users, is there, sir?
MR. SLATER: Objection.
MR. PARKER: 13.7 to 13.
THE WITNESS: Agreed.
BY MR. PARKER:
Q. And there is no difference in the composite endpoint for olmesartan versus other ARB users, 10 out of 20 versus 9 out of 20.
A. Uh-hum.
Q. Right?
A. Agreed.
Q. And the group with the highest responses to the composite outcome is actually the controls, 12 out of 20.

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A. Agreed.
Q. Is there any discussion in this paper that the group that achieved the highest scoring in the composite outcome was actually the controls?
A. Well, you can't compare the controls from one data group to another -- in other words, the matched controls that you're talking about that have the 12 of 20 were matched to the other ARB users. They weren't matched to the olmesartan users. They had different -- they're a different group. They had different -- the genders at least were fairly different.
Q. That may be true, but my question is, do you have any discussion in here about the observation that the group that had the highest response to the composite endpoint was the controls?
A. I don't see that here and I don't remember that. I also don't think that -- you know, that is a different -- it's a different group. It's a different

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population.
Q. Doctor --
A. I'll make one other point on that, if I may.
Q. If it's responsive to my question.
A. The group that was matched to the other ARB users, let's say instead of having 12 of 20 events in the composite, if they had had 1 of 20 and the olmesartan group was statistically significantly different, that would be completely unscientific to try to make that point after, as these are separate groups, with separate controls. You can't cross over controls like that.
Q. Doctor, are you familiar with the concept of a statistical trend?
A. Yes.
Q. You're not making the argument here that the number that you're relying upon, 10 over 20 over 4 over 20.1, represents a statistically significant trend.

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A. It is a trend --
Q. No, that's not my question. My question is, there are biostatisticians who can do statistical testing of difference in data, trending data; correct?
A. Yes.
Q. And you're not representing here that you had a biostatistician look at these numbers and say whether or not the result of .1 represented a statistically significant trend.
MR. SLATER: One second. I object. You've been -- you're switching your terms from question to question. You may not realize you're doing it or you may, but I object to this whole line because you are jumping back and forth.
You can answer.
MR. PARKER: Okay. Object.
THE WITNESS: The way I understand statistics is that commonly used parameters would

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indicate that .05 is statistically significant and .1 is considered a trend.
BY MR. PARKER:
Q. Okay.
A. Significant difference versus trend.
Q. Is .5 a trend to .05?
A. .5 to .05?
Q. Yeah.
A. Well, .5 would mean that there's a 50 percent probability that your results are due to chance, so, no, I don't think anyone would ever say .5 is a trend.
Q. What I'm not understanding, Doctor -- let's look at your P values here.
A. Uh-hum.
Q. How does .1 become any more of a trend than .4, .7, .3, .2, various different findings that you -- how does .1 become a trend?
A. It's a convention. It would

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imply that there's a 10 percent chance that this event happened randomly.
We in medicine generally would say less than 5 percent is considered statistically significant. Many people would say that .1 or 10 percent is a trend, but does not reach significance. Nobody would say 47 is a trend.
Q. .47 you mean.
A. .47, which would be a 47 percent chance of --
Q. So your answer to me, scientific convention is 10 percent difference represents a trend.
A. Yes.
Q. .1 to .05.
A. .1 to .05, yes.
Q. Thank you. Let's put that one aside, go on to the next one.
A. I'm just going to grab some water. We can keep talking.
MR. SLATER: Off the record.
- - -

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(A discussion off the record occurred.)
- - -
(A recess was taken from 3:55 p.m. to 4:10 p.m.)
BY MR. PARKER:
Q. Doctor, I want to go back just for a moment to your 2016 paper, which is Exhibit 10 in front of you.
A. Okay.
Q. According to your -- the disclosures on this paper, you submitted -- revised and submitted the manuscript on November 22nd, 2015?
A. Okay.
Q. By that time, you were consulting with Mr. Slater. Did you disclose that to the editors of this journal?
A. I did not. I don't believe it was required in this case.
Q. What do you mean "in this case"?
A. I don't believe that this

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journal requires disclosures of consulting work.
Q. Okay.
You're not suggesting that it might be of interest to readers to know that the authors of a paper are consulting as experts with plaintiffs' attorneys in the litigation, are you?
MR. SLATER: Objection.
You can answer.
THE WITNESS: Well, I couldn't really speculate as to whether it would be interesting to the readers or not, but I can say that the reason I wrote this paper did not have anything to do with consulting work.
It was, as I said before, to clarify the histologic differential diagnosis of this entity, and that's -- that was my motivating factor to do this.
BY MR. PARKER:
Q. I appreciate the reason why

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you were motivated to write the paper. My question is a little bit different.
If a scientist had written a paper concluding that the evidence fell short of establishing a causal connection and such an expert were consulting with Daiichi in this litigation, would you expect as a reader of that journal article to -- for them to disclose that?
MR. SLATER: Objection.
You can answer.
THE WITNESS: In that case, yeah, I would want to know that.
BY MR. PARKER:
Q. And would that not apply to you as well?
A. Well, in the first instance, I would say that causation really was not the focus of this article and it really didn't occur to me that there could be any bias in this. I don't feel like there was any bias in this.
Q. Okay. In response to my -- well, never mind. Let me move on. I

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think you told me what you can tell me about that.

I want to ask you to pick up the Mayo Clinic paper again and that is Exhibit 8 for your benefit.

A. Okay.

Q. And just to lay a foundation here, if we go back to that table 3 we talked about earlier --

A. Uh-hum.

Q. -- I think you will agree with me that while you may disagree, the Mayo Clinic takes the position that before you can assign a diagnosis of sprue-like enteropathy to someone taking olmesartan, you have to rule out other causes of enteropathy, including celiac disease.

MR. SLATER: Objection.

You can answer.

THE WITNESS: I would say that that is consistent with their published documents.

- - -

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(Deposition Exhibit No. Lagana-13, 2014 Paper "Sprue-like Enteropathy Associated with Olmesartan" by Cartee and Murray, was marked for identification.)

- - -

BY MR. PARKER:

Q. Now let me turn then to our next exhibit, which is Exhibit 13. This is a paper that was on your supplemental reliance list. For the record, it's a paper by Cartee and Murray, November 2014.

Have you read this particular paper?

A. I have.

Q. This paper reports that some number they don't disclose of their patients in whom they diagnosed sprue-like enteropathy they concluded most probably really did have celiac disease because of the reaction that they had when they resumed taking gluten; correct?

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MR. SLATER: Objection.

You can answer.

THE WITNESS: Can you tell me where you're reading that?

MR. PARKER: Yeah, sure, page 4 of 8. On the right-hand column, towards the upper part of the page where it states, "After the diagnosis and treatment for OAE," if you want to read that paragraph to yourself.

THE WITNESS: Page 4 of 8 and what part?

MR. PARKER: Upper right-hand column, where it says, "After the diagnosis and treatment."

THE WITNESS: Ah.

(Pause.)

MR. SLATER: Is the question just does he see that?

MR. PARKER: No. The question was, does he agree with me that some number of the

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patients at the Mayo Clinic who got a diagnosis of OAE, olmesartan-associated enteropathy, who had been thought to be not patients who had celiac, were later determined or thought to actually have celiac disease.

THE WITNESS: Well, I would agree that that is what is stated here. I would not necessarily infer that that relates to the series of 22 patients described in Rubio-Tapia.

BY MR. PARKER:

Q. And what leads you to think for the moment that this statement doesn't apply to at least some of the patients in the 2012 paper?

A. Why would I -- I mean, why would I assume that it does?

Q. Well, let's address it this way: Putting aside whether the people that they're referring to here were in the group of 22 or in their larger cohort

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of patients that they've seen for sprue-like enteropathy -- okay?
A. Uh-hum.
Q. -- what is said here -- let me read into the record the sentence you and I are talking about.
A. Okay.
Q. Cartee and Murray -- and Murray is the senior -- the contemporary, so to speak, of Peter Green at your institution. Right?
A. Correct.
Q. -- they write, "After the diagnosis and treatment for OAE" -- now let me stop there.
By their criteria, that means they had to have been satisfied that the patient did not have celiac disease.
A. I think that we're reading too much into what's in this article to say that. We don't know where these patients were worked up, where that diagnosis was made, or what workup went

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into those patients.
Q. My question is, their criteria for diagnosing OAE requires the exclusion of other causes of enteropathy, including celiac disease; correct?
A. They have published that.
Q. And what this statement is stating is, "After the diagnosis and treatment for OAE, several patients seen at the Mayo Clinic likely had underlying celiac disease as evidenced by symptoms with reinstitution of gluten into the diet and strong family history of celiac disease."
Now, let me stop there. Are you reading that sentence to say that someone other than the Mayo Clinic gave these patients the diagnosis of OAE?
MR. SLATER: Objection. You're twisting questions and answers.
THE WITNESS: I didn't say that that -- that's a possibility. I will say that that's a

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possibility.
BY MR. PARKER:
Q. Okay.
If the authors of this paper are talking about their patients for whom they made a diagnosis of OAE, who then had symptoms of enteropathy upon reintroduction of gluten, then by their written criteria, that person wasn't deserving of the diagnosis of OAE; correct?
MR. SLATER: Objection. You can answer.
THE WITNESS: Well, that can be interpreted in different ways. Another way that one could interpret that question, which involved quite a specific scenario, is that the patient came in, did not have celiac disease, was diagnosed with OAE, and after recovering from the OAE, since that's part of their published criteria for diagnosing OAE, as a

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response, later developed celiac disease. And in that case, perhaps -- perhaps olmesartan caused or exacerbated their celiac disease.
BY MR. PARKER:
Q. What do you understand the words to mean "likely had underlying celiac disease"? Are you reading that to say they had newly initiated celiac disease?
A. Well, celiac disease can be active or latent or potential celiac disease. They don't specify. But if you want to go down this very -- making a ton of assumptions about this -- we're making a lot of assumptions about these patients, including maybe their -- maybe they're the same people in Rubio-Tapia, were they diagnosed at Mayo Clinic, how exactly were they diagnosed -- if we're going to make a lot of assumptions and hypothetical scenarios, one of those hypothetical scenarios is that the

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patient had latent or potential celiac disease and that olmesartan turned it to active.

I'm not making that claim. But I'm just saying, if we want to go down a road of hypotheticals, there are a lot of possible hypotheticals.

Q. And when you read this paper and read that paragraph, did you not stop and say, wait a minute, maybe they misdiagnosed patients with OAE if, in fact, they really had celiac disease, underlying celiac disease, the phrase that's used here?

A. I don't draw the connection that these patients in Cartee are the same patients as in Rubio-Tapia.

Q. I'm not trying to make that connection, sir. I'm saying simply --

MR. SLATER: You're not? Everybody in the room thought you were, man.

BY MR. PARKER:

Q. I'm saying that they're

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describing patients that they saw at the Mayo Clinic. I care not from my questions whether they're the 22 or others.

My question is, when you read this, did you not say, wait a minute, how did they reach a diagnosis of OAE if, in fact, these people had underlying celiac disease? Did that ever occur to you when you read this paper?

MR. SLATER: Objection.

You can answer.

THE WITNESS: Well, I think the interplay between celiac disease and OAE is very interesting. I do wonder if -- not just for the purposes of being difficult, I do scientifically wonder if olmesartan can induce active celiac disease in patients with potential celiac disease. I don't know. I certainly don't know it to a medical degree of reasonable certainty. I have no

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idea. But it's an interesting speculation.

So when I read this paragraph, I leave open the possibility that the Mayo Clinic misdiagnosed them. I also leave open the possibility that they have both conditions or the possibility that one condition induced the other.

I don't think that these patients have been described in enough detail for us to draw conclusions about them and so I think that it's really just, you know, speculative.

BY MR. PARKER:

Q. Doctor, you don't hold the opinion, I think you just said, but I want to make sure the record's clear, to a reasonable degree of medical probability that olmesartan causes celiac disease.

A. Correct.

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Q. Okay.

Doctor, in your --

A. But I left open the possibility. We don't know yet.

Q. Anything's possible, Doctor. I just want to talk about what is reasonably probable. Okay?

A. Okay.

Q. Doctor, is there any -- or strike that.

Going back to your report, there's no discussion in your report of any evidence known to you demonstrating a dose-response between olmesartan and sprue-like enteropathy, is there?

A. In my report?

Q. In your report, sir.

A. Let's take a look. Well, in my report and to the best of my knowledge of the medical literature, there is no specific dose-response relationship, although there is a cumulative dose-response relationship as evidenced by Basson where exposures of greater than

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three years were associated with a tenfold risk of celiac disease.
Q. You said accumulated dose. Is it your understanding that olmesartan is retained and is built up in the body?
A. No, but accumulated exposure.
Q. That's different than accumulated dose. Right?
A. Yep.
Q. And if I'm not mistaken, there's no discussion in your report of any data that you have reviewed regarding animal studies.
A. There's no -- I don't believe that I referenced any animal studies.
Q. And have you, since your report was finalized on November 30th, done any reviews of animal studies looking at olmesartan and enteropathy?
A. I don't believe that I have.
Q. Let's move then to your discussion earlier, your reference to

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mechanism of action, if we might. Okay?
A. Uh-hum.
Q. Doctor, you said that you had come to the view that there was enough in the literature to lead you to conclude that this was -- "this" being olmesartan sprue-like enteropathy -- an immune-mediated condition.
A. Yes.
Q. Okay.
Doctor, is this a result of the innate or the adaptive immune system?
A. Well, they rarely act in isolation, but I think given the relatively long onset between exposure and syndrome, adaptive would have to be considered a large part of it.
But, again, they don't act in isolation. I'm not saying the innate immune system has nothing to do with it.
Q. And with respect to the adaptive immune system, is this predominantly a function of the humeral response or cell-mediated response?

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A. To the best of our understanding now, it's a cell-mediated process.
Q. When you say "the best of our understanding," I think you're -- are you talking collectively about those of you who believe there's cause and effect?
A. I believe that where the science is now, based on the prevalence of MHC, DQ2, DQ8 in the olmesartan enteropathy patients, the increased CD8+ T cells that have been demonstrated, and some of the cytokine perturbations, it's -- the scientific evidence appears to be pointing to a cell-mediated immune process.
Q. When you say the scientific evidence, are you speaking of anything more than the Marietta paper?
A. There have been other papers that have looked at the DQ2/DQ8 haplotype in olmesartan patients.
Q. Okay. That's what you mean by -- okay. Fair enough. Let's talk

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about that for a second.
A. Sure.
Q. Is this a function of an MHC or MH2 involvement, "this" being this cell-mediated response to olmesartan?
A. Could you repeat your question, please?
Q. Yes. You said it was a cell-mediated response.
A. Uh-hum.
Q. Does that involve MHC1 or MHC2? And I presume you know what those are.
A. I do.
Q. Okay.
A. I think it's an overly specific question for where we are at the moment. We know that HLA-DQ2 and DQ8, which affect the MHC molecules, are involved and I think beyond that, I'm not sure that -- I don't think we as a scientific community know that. I don't know that.
Q. Fair enough. Is it within

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your area of expertise to know whether HLA-DQ2 and 8 are involved with MHC or -- MHC1 or 2?
A. They certainly are involved. I don't recall if it's 1 or 2.
Q. Now, what we've been --
A. I think it's 2.
Q. Okay. What we've been talking about is a component of a cell that presents an antigen to the surface of the cell; correct?
A. Uh-hum.
Q. Again, that's a --
A. Oh, sorry. Yes.
Q. Okay. So, Doctor, what is the antigen that's being presented to the cells, be it MHC1 or 2?
A. That has not been discovered yet.
Q. So you don't know that either yet. Right?
A. Correct.
MR. SLATER: Objection.
BY MR. PARKER:

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Q. So something is being carried by MHC1 or 2 to the surface of the cells that have ingested an antigen -- correct?
A. Well, I think that we're going -- we're getting ahead of the science here.
Q. Okay.
A. I think that -- first off, it's MHC2. I was a little foggy before, so let me just correct that --
Q. We'll take that.
A. Yeah -- and then let me say, if you look at a disease like celiac disease, you know, we knew that gluten was the inciting cause of celiac disease for probably 20 years before we understood these immune interplays that you're now getting at.
So I think that for a disease that was discovered in 2012, to say, well, if we can't tell precisely what antigen is expressed by what innate immune cell to what part of the -- to

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what T cell and what exact -- you're putting an unreasonable burden on the scientific community to answer that question.
Q. Is it your theory that olmesartan is the antigen?
A. I think there are a number of possible mechanisms at the cellular level. I think that we know that olmesartan exposure leads to inflammation which is T cell rich --
Q. How do we know that?
A. The totality of the published work has shown increased CD8+ T cells.
Q. Okay.
A. Okay? And what the exact -- the Marietta paper implies -- or plausibly suggests -- they're all for IL15; but, again, going into the cytokine milieu of this process four years or so after the process was discovered, to be honest, I think it's a red herring. I think it's similar to -- I could say it's

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probably half a century that we knew cigarette smoking caused lung cancer before we understood precisely what cellular alterations were going on in the cells of the lung to produce the lung cancer.
It really wasn't until the Human Genome Project was complete and we still don't know all of it. We still learn additional details every day.
So, you know, I know that in some patients who have olmesartan exposure, they get inflammation of the GI tract which is characterized by lymphocytes, plasma cells, sometimes intraepithelial lymphocytes, sometimes not, neutrophils, eosinophils, sometimes fibrosis, sometimes not, sometimes villous atrophy, sometimes not; and that this causes these people a number of very serious GI complaints; and that these patients get better clinically and histologically when they stop taking olmesartan.

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MR. PARKER: Move to strike. Let's go back to my questions about --

MR. SLATER: Just so you understand, when he moves to strike doesn't mean anybody's going to actually respect that in a courtroom, so you can just keep giving your answers.

MR. PARKER: Which is what you did with all my witnesses, too, but that's okay.

MR. SLATER: Well, mine were all valid motions to strike.

MR. PARKER: Okay. And you made a lot more of them than I'm making today.

BY MR. PARKER:

Q. Doctor, I want to go back to this mechanism concept. You're not aware, I take it from what you've said, of the studies that have been done looking at whether olmesartan in various tissues within the human body are

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pro-inflammatory or anti-inflammatory, are you?

MR. SLATER: Objection. You can answer.

THE WITNESS: I'm not particularly familiar with those studies.

BY MR. PARKER:

Q. And if studies were to demonstrate that olmesartan reduces inflammation, that would be inconsistent with your theory that olmesartan is somehow causing sprue-like enteropathy.

MR. SLATER: Objection.

THE WITNESS: No, because I'm not sitting here saying to you that olmesartan is poison and everyone who takes it is like cyanide, no; but in some patients, I believe that it has a deleterious effect and that it directly causes the histologic changes and the clinical symptoms that I just described.

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So it could be that -- if you look in a monkey model or a mouse model or even across plenty of patients, it could very well be true that in some organ systems or in some patients, it has anti-inflammatory properties. It could also be true that in some patients, it causes everything I just said it caused.

BY MR. PARKER:

Q. Doctor, in anybody who has enteropathy, you would expect an increase in CD8 cells; correct?

A. In the vast majority of the patients with enteropathy.

Q. So all of the things we've been talking about today, celiac disease, unclassified sprue, autoimmune enteropathy, and the whole list, not to repeat them all that we've talked about, are all conditions that are characterized by inflammation of the small bowel in one way or the other; correct?

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A. Yes.

Q. And all of those, because they involve inflammation and immune responses to some stimuli, are going to result in increase in CD8+ cells relative to someone who is, quote, normal and not symptomatic.

A. Yes.

Q. So if someone comes into the hospital and said, "I have enteropathy, I also happen to be taking olmesartan," it shouldn't surprise you at all that they have an increase in CD8+ cells.

A. Right, because the olmesartan is causing the inflammation.

Q. And what is the cause of the inflammation -- well, forget it.

You mentioned IL15. In anybody who has enteropathy and an increase in CD8 cells, would you not expect an increase and upregulation in IL15 receptors?

A. In patients who have inflammation, that's a common finding,

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yes.
Q. Right. So when people come in your door before you know anything at Columbia and they present with symptoms of enteropathy, you can make a pretty good guess that they're going to have increased CD8 cells and increased IL15 receptors if you do cytometry. Right?
A. Correct.
Q. All right.
So just so the record's clear, there is nothing unusual at all with people who have enteropathy who happen to be taking olmesartan who have an increase in CD8+ cells and IL15.
A. "Nothing unusual" is really an impressive statement. No, it's very unusual. They have inflammation. They have villous atrophy. They have fibrosis. They are highly unusual patients. They are damaged, sick people --
Q. Compared to normals.
A. Yeah.

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Q. But, I mean, within the world of people who come into Columbia with enteropathy, that's not a surprising presentation, that someone who comes in with enteropathy, you would expect to have CD8+ cells and IL15 receptor increases.
A. Somebody who has a debilitating intestinal illness, whether it's caused by olmesartan or gluten, yes, I would expect those particular -- you would find those cytokine changes.
Q. And we can expand up and down that to autoimmune enteropathy, tropical sprue, and the like.
A. There are differences between those.
Q. Of course there are differences, but you would expect to see CD8 increases, CD8+ cell increases, and IL15 receptor increases.
A. I'd have to check the data, but I don't have a problem with that.
Q. Okay.

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Now, you talked about cell-mediated response is your theory about how olmesartan, in your opinion, may lead to enteropathy in some small number of people. Right?
A. Correct.
Q. Is this -- which of the types of cell immune responses are you talking about specifically? Are you talking about a delayed type hypersensitivity reaction, a Type IV reaction?
A. I'm not sure and I'm not sure that we know yet.
Q. Well, if it's not Type IV -- there's only four types as far as I know -- am I wrong -- of -- of adaptive immune responses?
A. I'd have to check the --
Q. Okay.
A. But I -- again, I think that you're pushing me to be more specific than I'm ready to be on the pathogenesis. I don't know that we as medical science

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are quite there and I don't think that we need to be to know that, as I said before, in some subset of patients who are exposed to olmesartan, they get inflammation of the intestine, they get potential sequelae of that, like villous atrophy and fibrosis, and they have the clinical symptoms I've described several times.
- - -
(Deposition Exhibit No. Lagana-14, 2015 Paper "Immunopathogenesis of olmesartan-associated enteropathy" by Marietta, et al, was marked for identification.)
- - -
BY MR. PARKER:
Q. Let me move on to the paper you have mentioned several times today, Marietta, Exhibit 14. Now, this one was cited in your report; correct?
A. I believe so. Yes.
Q. And, Doctor, am I correct

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that this is the paper on which, not exclusively, but you primarily rely to say that there is a reasonably plausible mechanism that explains how olmesartan causes enteropathy in some people?

A. Mechanism can mean different things, so I think this is one of the few papers or maybe the only paper that has gotten to the cytokine and molecular mechanistic level, so, yes, this is a paper that would inform that understanding.

Q. My question was, is it, not exclusive, but the primary paper on which you rely for the mechanism of action?

A. I'd have to think about that for a second.

Q. Sure.

(Pause.)

THE WITNESS: No, I think if we have an immune-mediated inflammatory process, which is what I understand it to be, that's based on the totality of my

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reading and my experience looking at inflamed biopsies.

If you're asking me about molecular mechanisms, this is probably the only one that I would rely on to talk about the molecular mechanisms at the very minute cytokine level.

BY MR. PARKER:

Q. Doctor, you've never done an experiment with CACO cells?

A. I have not.

Q. You understand, however, they are cancer cells of the colon?

A. I believe that's correct.

MR. SLATER: Objection.

You can answer.

BY MR. PARKER:

Q. Doctor, what results -- so I -- maybe I'll save some time. What results in this study do you find supportive of your view that there is an immune mechanism stimulated by olmesartan?

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A. Okay. First point is that there are more CD8+ T cells in the on-olmesartan group than in the off-olmesartan group. That's statistically significant.

There are more FoxP3+ cells, which are regulatory T cells, supposed to be inhibitive of formation. That's also statistically significant. And the same for IL15.

(Pause.)

THE WITNESS: It will take me a few more minutes to get through the rest of it, but the points that have just been made demonstrate abnormalities in the inflammatory response in the on-olmesartan group compared to the off-olmesartan group.

And, furthermore, I think that this paper is important to start -- in our beginnings of understanding the molecular mechanisms of this, but I would

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again go back to the analogy of lung cancer and smoking. We made the association between smoking and lung cancer long before we knew about EGFR mutations, KRAS mutations, P53 mutations, and so on and so forth.

If you'd like, I could take a few minutes and read more about the ZO1. I'd have to remind myself what the conclusion was regarding ZO1 --

BY MR. PARKER:

Q. By the way, you keep referring to your tobacco/cigarette example. That causal -- association then causal association was demonstrated through epidemiological research, not case reports. Right?

A. Ultimately.

Q. Ultimately, right.

A. Ultimately, but it didn't start that way --

Q. That's not my question.

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A. -- AIDS was described in a case report.
Q. My question was, using your example that you've used in cigarette smoke, you say, well, we know what caused it and we didn't know the mechanism.
And the reason the scientific community agreed that there was a cause and effect was based on epidemiological research and a lot of it; correct?
MR. SLATER: Objection.
THE WITNESS: The point I'm trying to make is --
MR. PARKER: Will you answer my question?
MR. SLATER: Objection because there's a huge foundational flaw.
You can answer.
THE WITNESS: Mechanism speaks to many different levels and you're asking about the most minute of levels, and I'm pointing

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out that it was half a century with the cigarette smoking phenomenon that we knew about the causal effect of cigarette smoking before we knew the molecular biology to the extent that you're asking me about it today.
BY MR. PARKER:
Q. But my question is, the scientific community reached a conclusion of a causal relationship based upon epidemiological research, not case reports.
MR. SLATER: Objection.
You can answer.
THE WITNESS: I think both were important; and in this case, we do have not only the case reports, but we have the French study, which was a large epidemiologic study, that did show a clear signal.
MR. PARKER: Move to strike.
BY MR. PARKER:

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Q. Doctor, let's talk about -- you said on and off. Now let's talk about how this study was actually done.
A. Okay.
Q. They tell us that they had seven people in whom they had biopsy samples both while on olmesartan and off; correct?
And then they had 26 samples of 11 people who were on and different people who were off.
MR. SLATER: You're asking him to tell you whether that's right or not or are you just reading the article to us now, Bruce?
MR. PARKER: No, I'm not. I'm asking him -- he -- this is Dr. Lagana's primary piece of mechanistic literature. I want to make sure I understand.
BY MR. PARKER:
Q. You said on and off. The conclusions that this group drew were

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looking at one group of people who had been on and another group of people who were off, not the paired samples. Am I correct?
A. First, I don't think I said this is my primary --
Q. I'll withdraw that "primary."
A. Thank you. So let me please read through it and then I will respond to your question, which is a very detailed question, which I haven't memorized.
MR. SLATER: Which I'm objecting to, just for the record, on the form.
(Pause.)
THE WITNESS: Can you tell me where you found that information?
BY MR. PARKER:
Q. Well, I'm starting first at the extraction of the duodenal biopsies. They tell us that there were seven paired

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samples, meaning somebody had a sample taken while they were on drug and off the drug, and then they had 14 other samples, 4 on and 10 off. That's all laid out in that paragraph there; correct?
A. The one that says extraction of duodenal biopsies.
Q. Yes, sir.
A. Okay. Let me read it.
(Pause.)
THE WITNESS: Okay. Yes, I agree with the way you've characterized the patients.
BY MR. PARKER:
Q. Now, the first thing that you drew my attention to was the CD8 findings; correct?
A. Uh-hum.
Q. Now, if we turn to page 3 under distribution of CD8 cells, that's the section you're relying upon. Right? Those are the results?
A. Those are the results, yes.
Q. They don't look at the

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paired samples and would you agree that that would be more informative than someone who was on and someone else who was off, two different people?
A. I would like to know that information. I don't know that I would specifically say that -- if they only had seven paired patients, that's a small sample size, so I understand bringing other exposed or unexposed patients into it and I think it's still meaningful.
Q. Doctor, all things being equal, it's more informative to get results from paired samples than unpaired samples. Would you agree with that basic proposition?
A. You used the term "better"?
Q. More informative.
A. More informative.
There are benefits both to having paired and unpaired samples. I would like to know that information, as I've said, and I agree that that would be interesting information as well.

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I'm not sure that -- you get individual variations that can be corrected for by having unpaired samples, so I think that there are benefits to both paired and unpaired.
Q. Tell me what benefit in a scientific experiment like this looking at the distribution of CD8 cells on and off olmesartan -- what benefit would you have with an unpaired sample compared to paired?
A. You get a more population-based look at it. If everyone is paired, I would still want to see the cumulative data, because I think the cumulative data tells you something different than the individual data tells you.
Q. We can agree in this case they used the unpaired samples for their analysis of CD8; correct?
A. Are you implying that they excluded the paired samples?
Q. Doctor, I'm simply asking if

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you agree with what they say, the analysis was done on unpaired samples, 11 on olmesartan, 17 off.
A. Okay. I agree.
Q. Now, Doctor, nowhere in this paper did these investigators attempt to control for other drug usages by these unpaired samples; correct?
A. Well, let's see.
MR. SLATER: You can take your time and find it.
MR. PARKER: I'm not rushing him.
(Pause.)
THE WITNESS: Okay. I do not see a reference to other drugs.
BY MR. PARKER:
Q. Doctor, they also -- "they," the investigators in this paper -- also looked at transforming growth factor beta; correct?
A. I believe so, yes.
Q. In fact, that was a theory

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that the Mayo group put forth in 2012 when they first presented their case series of 22 patients.
A. I recall that being at least one theory. I don't know if that's the only one that they mentioned, but --
Q. And this paper found that there was no support for that theory.
A. I believe that's true.
Q. And this paper found that FoxP3 cells were upregulated in people on olmesartan; correct?
A. I believe that's true. Let me double-check that.
(Pause.)
THE WITNESS: Correct.
BY MR. PARKER:
Q. And FoxP3 cells are cells that are -- the body makes when it's attempting to turn off inflammation in the body.
A. That's our current understanding of the main role of the FoxP3+ T cell, yes.

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Q. So you would want to see in someone with inflammation an increase in FoxP3 cells.
A. What do you mean by "want to see"?
Q. Well, if you want to turn off the inflammation that somebody is experiencing, would you not want their body to be producing more cells that have a down regulatory effect on inflammation?
A. Well, that would depend on the cause of the inflammation.
Q. Well, you haven't told me how olmesartan is causing inflammation, have you?
A. Well, again, if you're getting to the molecular mechanism by which olmesartan -- the molecular mechanism by which olmesartan causes inflammation, I would say that we're learning about that. We don't know everything about that and it's an unfair bar to meet.
Q. You keep saying olmesartan

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causes inflammation. You reached that conclusion because, clinically, people have enteropathy who are on olmesartan; your experience, as you told me, they go off olmesartan and they get better, and thus you conclude that olmesartan is causing the inflammation in that person; correct?
MR. SLATER: Objection. He never said that was the sole basis for his opinion. Come on.
You can answer.
THE WITNESS: Okay. Well, that's part of my -- of the basis for my opinion, absolutely, my clinical experience has shown me that.
There are other -- I've also seen case reports of dozens or more patients who have similar findings, including inflammation, often that was demonstrated to have resolved off olmesartan.
And the Basson study which

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I've referenced several times shows an epidemiologic effect, so, I mean, we can -- you say, well, isn't it expected that FoxP3 would be upregulated, isn't it expected that CD8 would be upregulated, yes, in a person who is inflamed.
BY MR. PARKER:
Q. For FoxP3 cells, I said you would want to see them upregulated in someone who has inflammation for whatever cause.
A. Okay. And that's incorrect, because in some cases, if someone had an infection or something, you don't want to turn off the immune system FoxP3 cells. You would want to see them increased.
If there was something like an autoimmune-type reaction, then yes.
Q. Okay. Or celiac disease; correct?
A. Correct.
Q. Okay.
A. Celiac disease is an

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autoimmune disease.
Q. What is the connection between IL15, if you know, and CD8 cells?
A. Yeah, let me refresh my memory.
(Pause.)
THE WITNESS: IL15 and IL15 receptor are important in the T cell reaction and the T cells -- CD8+ cells are T cells, so they're part of the same pathways.
BY MR. PARKER:
Q. What does that mean, they're part of the same pathways?
A. IL15 and IL -- IL15 is a cytokine. It has an effect on attracting other cells. I believe it attracts T cells. I can double-check that if you want to get more in-depth on IL15.
Q. So in some way, IL15 -- well, let me back up. Does IL15 cytokine, is it secreted? Does it exist in the plasma?
A. Cytokines are secreted, so

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yes.
Q. Specifically IL15.
A. I would assume so. I don't know exactly if it's --
Q. If I'm outside your area, just tell me. I'm going to move on. Am I outside your area?
A. I'm not an immunologist, so it is possible to get out of my depth on immunology.
Q. Have I just gotten out of your depth talking about IL15 and whether it's secreted, whether it's present in the plasma?
A. Yes.
Q. Okay. See, very easy.
A. Okay.
Q. Now, let's go back to this paper, and part of this paper talks about CACO cells in tight junctions.
A. Uh-hum.
Q. Now, I want to make sure I understand before I leave this paper, are you placing any reliance on the results

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of this study from CACO cells in tight junction?
A. Allow me a minute to just --
Q. Please.
A. -- refresh the story about the tight junctions.
(Pause.)
THE WITNESS: I think the tight junction story is interesting.
BY MR. PARKER:
Q. Do you rely upon it for your opinion that there is a plausible mechanism that has been established through scientific study?
A. Minimally.
Q. Minimally. Okay.
Turn to figure 6, please -- we'll leave CACO and tight junctions for another day.
A. Okay.
Q. -- let's turn to figure 6. Figure 6 is telling us how these investigators were able to measure the

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level of IL15 receptors in their CACO cell experiments; correct?
A. Yeah, if you don't mind, I'd like to look at our copy of this, because this (Indicating) is a little bit --
Q. I'm actually not going to look at the diagrams, but please pull out your own copy if it's better.
MR. SLATER: It should be at 33.
THE WITNESS: 33. Okay. Figure 6.
MR. PARKER: Yes, sir.
THE WITNESS: Okay.
BY MR. PARKER:
Q. Now, you see that what they were doing here is, they were applying a certain concentration of three different ARBs, olmesartan, losartan, and telmisartan, to these CACO cells and then measuring the level of IL15 receptors; correct?
A. Okay. Correct.
Q. Now, when you read this, did

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you ask yourself, well, what is the relative concentration or dosing, if you will, between losartan, telmisartan, and olmesartan in people? Are they the same or is there a difference in dose in the human?

A. I did not ask myself that question.

Q. Do you know which one is the lowest?

A. I do not know.

Q. Okay.

And without knowing that, you don't know whether this given concentration of each one of these drugs is more disproportional for one than the other in terms of the physiologic load that someone sees when they take the drug.

A. This is a cell line study. This is -- to me, this is too far removed from the clinic to draw direct --

Q. I know, but can you answer my question? Without knowing whether the

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dosing that are -- that -- the maximum dose for olmesartan, losartan, and telmisartan are the same or different, you won't know whether this concentration that was the same concentration used for all these drugs would have a disproportionate effect from one drug to another.

A. I would expect that the peer reviewers of this article would have addressed that.

Q. I'm asking you, sir. As you read this paper --

A. Well, I -- no, as I said, I would expect that whoever peer reviewed this would have assumed -- would have confirmed that it was appropriate.

Q. I see. So you've never -- well, let me ask you directly: Do you know what the plasma concentration of olmesartan is in the human?

A. No.

Q. So without knowing the plasma concentration of olmesartan, you

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don't know what the concentration is used here, whether it's comparable to what a human might see taking olmesartan or vastly increased from what someone will see when they take olmesartan, do you?

A. I would presume that the peer reviewers of this reputable journal would have confirmed that the study design was appropriate.

Q. That's not an answer to my question. My question is, without you as a scientist doing a review of this paper as part of the work in this case, you personally don't know how 30 -- and this is -- on figure 6, this is 30 micromoles, right, that's what that symbol stands for?

A. Uh-hum.

Q. U-M-O-L?

A. Yep.

Q. 30 micromoles per liter of losartan, olmesartan, and telmisartan, that's the concentration that was used. Right?

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A. Uh-hum.

MR. SLATER: Objection.

You can answer.

BY MR. PARKER:

Q. Let's focus just on olmesartan. Do you know what the maximum dosing is of olmesartan in the United States?

A. 40 milligrams a day.

Q. And what you're not able to tell me right now is whether 30 micromoles per liter of olmesartan -- how that compares to someone who gets 40 milligrams of the drug.

A. I'm not a basic scientist. This paper was peer reviewed and published in a fairly prominent journal. It's my understanding that papers that are published in peer-reviewed journals like this have gone through a peer-review process and that the study design is appropriate. If it's not, someone should publish a counterargument.

Q. But, Doctor, my question to

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you is, you don't know -- I'm not talking about peer reviewers. You don't know that, do you, sir?
A. I don't know that, nor do I think I should be expected to. It's published in a prominent journal.
Q. Do you know what the impact factor of this prominent journal is?
A. I don't, but I've seen the journal many times. Do you know?
Q. Have you ever published in it?
A. No.
Q. Is it a paid for publication journal?
A. I don't know.
Q. Doctor, if I were to tell you that 30 micromoles per liter of olmesartan is approximately 20 times greater than any human will ever get taking olmesartan at 40 milligrams, would it say that maybe these results are not physiologic?
MR. SLATER: Objection.

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You can answer.
THE WITNESS: I couldn't say. It would really depend if this is standard for studies like this, and that would be reliant on a peer reviewer who is an expert at this type of experiment to say.
BY MR. PARKER:
Q. Let me -- let's talk about one other question as long as we're talking about peer reviewers. Let's see if I can find it. Bear with me. Okay.
Doctor, if we look at figure 6, as we have been, the concentration that's said to be used is 30 micromoles per liter. Right?
A. Correct.
Q. Then if we go back to the next page, figure 7, another part of this experiment, again they talk about 30 micromoles per liter of olmesartan that's used.
A. Okay.
Q. Right?

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A. That's what it seems to say.
Q. And then in figure 8, we see 30 micromoles per liter of olmesartan. Right?
A. Okay.
Q. Now, those are all statements that follow page 5 of this report; correct?
A. So those are all after page 5, you're saying?
Q. Yes.
A. Yes.
Q. And if we look on page 5, what actually appears in the text that these peer reviewers would have looked at is that olmesartan medoxomil was used at 30 millimoles per liter. Do you see that? On the right-hand side. And they actually reference figure 6.
A. 30 micromoles per liter, yes, that's --
Q. No. MM is millimoles.
A. Oh.
Q. Correct?

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A. Okay. Yeah, you're right. MM, millimoles.
Q. How much larger is a concentration of 30 millimoles compared to 30 micromoles?
A. A thousand.
Q. A thousand times.
A. Yeah. So it's a typo. I mean, we're fighting about the tree here and we're really ignoring the forest, which is that --
Q. Well, we're really talking about --
MR. SLATER: Hey, you know, he's talking and you're interrupting because you're arguing with him --
MR. PARKER: I'm not arguing --
MR. SLATER: Hey, wait. Hang on. You just interrupted him. Slow down. Bruce, it's not getting done soon.
MR. PARKER: Answer the

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question --
MR. SLATER: Hang on. Listen, you're going to use your time and I'm going to go and prepare for 45 minutes and then do my questions.
MR. PARKER: Right.
MR. SLATER: So just relax.
MR. PARKER: Doctor --
MR. SLATER: Wait. He was talking. You interrupted him. You're just not going to let him continue --
MR. PARKER: Are you going to talk for the rest of the night?
MR. SLATER: Every time you interrupt him --
MR PARKER: Then we'll go on longer than the seven hours --
MR. SLATER: No, you won't --
MR. PARKER: Doctor --
MR. SLATER: He was speaking -- hey --

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MR. PARKER: Don't tell me what I'm going to do.
MR. SLATER: He was speaking. You're going to let him finish his answer.
MR. PARKER: Sure, I'm going to let him finish the answer.
BY MR. PARKER:
Q. How much greater are millimoles than micromoles?
MR. SLATER: Don't answer -- finish your other answer, then you can answer whatever question he wants to pile on after.
MR. PARKER: So you're instructing him how to answer the question. That's good.
MR. SLATER: I'm telling him to answer the question. You interrupted his answer.
MR. PARKER: Go ahead, Doctor.
THE WITNESS: Okay. It is 1,000 times greater and it is --

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what I was going to say is, we're discussing -- you know, we're arguing about the color of the bark on one of the trees in Sherwood Forest and I think that it's trivial.
But, yeah it's a typo. There's a trivial typo --
BY MR. PARKER:
Q. In answer to a number of my questions about the experimental design of this study, your response to a number of those questions, well, I gotta rely upon the peer reviewers who will not allow this to be published unless it's the right experiment.
That's in essence what you were telling me. Right?
MR. SLATER: Objection; mischaracterization and foundation.
MR. PARKER: Right?
THE WITNESS: Well, I mean -- yes and, you know, you've --

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clearly there's a typo. What percentage of medical articles have typos in them, I don't know. I don't know that this has more typos than anything else or that this is, you know, specifically sloppy because there's one typo, which is clearly what the implication is, and again this is a minute part of my thinking on this topic.
BY MR. PARKER:
Q. Doctor, I just want to ask my questions about a paper that you've said and you relied upon in your report. Okay?
If this paper at 30 -- if the true value was 30 millimoles, not micromoles -- let me stop there. You don't know what the right concentration is. Right?
MR. SLATER: Objection. You can answer.
MR. PARKER: Sitting here

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right now.
THE WITNESS: I would acknowledge that it said two different -- it's said incorrectly at least once.
I would assume it's micromolar.
BY MR. PARKER:
Q. But you don't know that, do you, sir?
A. No.
Q. And if it -- if -- you don't know, but if 20 micromoles is 30 times greater -- excuse me. If 30 -- I'll start again.
If 30 micromoles is 20 times greater than a dosage of 40 milligrams in a human, then 30 millimoles is 2,000 times greater than what someone would ever experience taking olmesartan at prescribed dosages.
MR. SLATER: Objection.
You can answer.
MR. PARKER: Right?

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THE WITNESS: Okay.
BY MR. PARKER:
Q. Okay. Now, and as we talked about, as you read this paper -- and you said you read it --
A. I did.
Q. -- and you tried to determine whether this was reliable science -- correct?
A. Yes.
Q. Okay -- the issues that we're talking about, concentrations and dose, were not questions you asked yourself. Fair enough?
A. Right. I presumed that they were appropriate based on the fact that the paper was peer reviewed.
Q. If, in fact, the concentrations here were 20 times larger than what a person would see, is it your view -- and if it's outside your area, just tell me -- is it your view that that's an appropriate dosing to use to determine what a person taking olmesartan

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at 40 milligrams is likely to see happen in their body?
A. It's outside my area.
Q. Okay.
A. If that's standard, fine. If it's not, then someone should write a letter to the editor about it.
Q. Let's turn to a different area --
A. Can we do another five before we move on?
MR. SLATER: Yes.
MR. PARKER: Sure.
THE WITNESS: Okay.
(A recess was taken from 5:17 p.m. to 5:27 p.m.)
- - -
(Deposition Exhibit No. Lagana-15, 2015 Original Article "Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study" by Basson, et al, was marked for identification.)

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- - -
BY MR. PARKER:
Q. Doctor, let's go on with Exhibit 15, which is the Basson paper, a paper that you've mentioned a few times today. Okay?
A. Sure.
Q. And this is that French study that you have mentioned throughout the course of the day?
A. Correct.
Q. Have you discussed the methodology in this paper with any of your colleagues at Columbia who are trained in epidemiology?
A. I can't recall any specific discussions with my colleagues about the methods.
Q. And I want to make sure that I'm not assuming something that's incorrect. You've never been trained in the field of epidemiology beyond which you're exposed to in medical school; is that correct?

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A. That's correct.
Q. You certainly don't hold yourself out as being an epidemiologist.
A. I do not.
Q. Okay.
Now, is it within your area of expertise, in light of what we just discussed, to discuss the methodological strengths and weakness of this paper?
A. I believe so.
Q. Doctor, first off, there's no controlling in this paper for other drug use, is there?
A. Meaning other than other antihypertensives?
Q. I'll accept that, but, yes, I'm talking about other drugs that are known to either induce diarrhea or to prevent it.
A. I don't believe so.
Q. Is that a weakness of this study design?
A. In my opinion, that would only be a weakness if you expect that the

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rates of usage of diarrhea-causing or preventing medicines is different between olmesartan users and other users of ARB -- or users of other ARB; otherwise, you would expect that whatever contribution is there comes out in the wash.
Q. So I'm not sure that answers my question. You said "if." My question is, do you consider that to be a limitation of this study, a methodological limitation?
A. I don't consider it to be a significant weakness.
Q. This paper doesn't look at the endpoint of sprue-like enteropathy associated with olmesartan or olmesartan-associated enteropathy or any other name given to enteropathy in connection with taking olmesartan, does it?
A. So this is based on registry data and ICD coding, of which there is not an ICD code for olmesartan-associated enteropathy, so --

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Q. So I'm right.
A. You are correct.
Q. Okay. Thank you. All right.
Now, they do look at malabsorption. That's their primary endpoint; correct?
A. Sorry. I just sort of bumped my knee on the table.
Q. Ouch.
A. Give me a second. Yeah. Otherwise, my answers are going to get hostile.
All right. Please repeat your question.
Q. Sure.
The primary endpoint of this study was malabsorption.
A. I believe it was an ICD code of malabsorption or celiac disease -- the primary was malabsorption, yes.
Q. And that's my second question: The secondary outcome was celiac disease.

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A. Correct.
Q. Now, do you consider malabsorption -- strike that.
The -- an endpoint of malabsorption or diarrhea, for example, would be considered to be a surrogate for olmesartan-associated enteropathy or sprue-like enteropathy.
A. The ICD code for malabsorption I think is a reasonable surrogate for olmesartan enteropathy.
Q. Well, you were one question ahead of me, but my first question is, it's considered a surrogate and your answer to me is, you consider it to be a good surrogate.
A. Reasonable.
Q. Reasonable. Okay.
Is there a better surrogate to use to study -- to do an epidemiological study if you're looking at sprue-like enteropathy associated with olmesartan?
A. Assuming that we're working

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with registry data like these people were?
Q. Well, let's start there.
A. If you want to suggest a couple, I can tell you if I think that they're better --
Q. No, this one's all in your court, Doctor.
A. So you want a better surrogate --
Q. Is there? You said it is a good one, so my question is, is there a better one than malabsorption in your opinion?
A. Well, I think the ICD code for celiac disease certainly is another reasonable one. If it's better or not, I don't really think I have an opinion on that.
Q. Well, of the epidemiologic studies of which you are now aware, including Basson -- that's malabsorption; correct?
A. Uh-hum.

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Q. -- then you have Greywoode, which was diarrhea; correct?
A. I'd have to double-check Greywoode.
Q. Padwal was hospitalization for noninfectious GI disorders?
A. I'd have to double-check it as well.
Q. Okay.
And the Manhaller paper were a variety of GI endpoints.
A. Yes.
Q. Free to pick any other surrogate endpoint, but of that group, do you have an opinion as to which you consider to be the best surrogate for sprue-like enteropathy?
A. I would think that malabsorption, diarrhea, celiac disease, those are the ones that would come to my mind as the best -- or as a group of reasonable ones. As far as is one better than the other, I don't have an opinion.
Q. You left out GI

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hospitalization for noninfectious causes. Why would you consider that to be inferior to the other ones?
A. Well, I mean, so patients with colon cancer are going to be caught by that endpoint. It's a little bit less specific.
Q. Anything else, sir?
A. I have nothing else to add to that.
Q. Doctor, let's take a look at this paper and the authors of this study -- and you do embrace this as part of your causation opinion, you've told me a couple times today; correct?
A. I do.
Q. Okay. The authors report on page 1 -- report states -- excuse me -- these reports suggest that olmesartan may cause severe enteropathy; however, the level of evidence of case reports in small series is limited.
Now, this is a paper published after July of 2015. Do you

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agree that that's an accurate statement at the time this paper was published?
MR. SLATER: Objection.
You can answer.
THE WITNESS: I would agree that on the hierarchy of evidence, case series and case reports are on the lower end of that, so yes.
BY MR. PARKER:
Q. If you turn to the next page and the first full paragraph begins with "The association" -- do you see that?
A. Yep.
Q. -- and they write, "The association between olmesartan and enteropathy needs to be further investigated. The causality of the association remains uncertain and its magnitude has not been determined."
Do you agree with that statement at the time this was written in August of 2015?
MR. SLATER: Objection.
You can answer.

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THE WITNESS: Well, let's parse it a little bit, if I may.
The association between olmesartan and enteropathy needs to be further investigated, I would think anyone who cares about this topic would agree with that statement. No one would say we're done and close the book on this.
The causality of the association remains uncertain, that doesn't reflect my opinion --
BY MR. PARKER:
Q. As of August of 2015.
A. I believe that is accurate.
Q. I mean, I'm just trying to be fair to the authors. That's when they wrote this. Right?
A. Okay.
Q. Okay.
A. And the magnitude has not been determined, I agree.
Q. And by magnitude, what do you understand them to be saying?

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A. I would expect they'd be talking about the incidence, the increase of the relative risk.
Q. If you turn to table 1, tell me if I'm understanding this correctly, in their study, they looked at some 860,000 registry records for olmesartan users, out of which they found 48 cases of malabsorption; is that correct?
A. It's going to take me a minute to determine -- I agree with most of what you said. I need to clarify if this is just malabsorption or malabsorption and celiac disease they're referencing here.
(Pause.)
MR. PARKER: This might help you, Doctor. If you turn to the third page, the paragraph "Incidence of severe malabsorption and celiac disease"?
THE WITNESS: Uh-hum.
BY MR. PARKER:
Q. They report 48 cases of

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malabsorption?
A. Yep. I'm reading that and I'm just looking to see if they give a separate incidence for the celiac disease or if that's included in the 48 cases.
(Pause.)
THE WITNESS: Okay. I think that the number 48 reference to malabsorption does not include the celiac disease cases, so I would agree with your statement.
BY MR. PARKER:
Q. And, actually, they don't give us the number of celiac disease cases. They give us a relative risk, but not the number of cases; correct?
A. Okay. I'm going to have to check that again. I --
Q. Yeah, sure.
A. In that paragraph, I didn't see that. I saw the relative risk. I didn't see the --
MR. SLATER: He's just waiting for your answer. You can

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just look for it, take your time, and answer his question.
(Pause.)
THE WITNESS: Okay. I think that what you said is accurate.
BY MR. PARKER:
Q. Doctor, if we scroll down that column, we see them beginning to report on celiac disease, the relative risk. Do you see that?
A. You're talking about on page 4, underneath the table on the right?
Q. Actually, I'm looking at page 3 when it begins to discuss the results for celiac disease. Paragraph begins, "Hospitalizations with a discharge diagnosis of celiac disease," do you see that?
A. Yep.
Q. Okay. And if you just read that to yourself over -- it continues over, they report a relative risk of 4.82 for celiac disease occurrences between olmesartan and other ARB users; correct?

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A. Yep.
Q. What does that mean, 4.82?
A. It means that if we take the other ARB users to be the controls, if we said 1 out of -- these are made-up numbers and totally inaccurate, but if we said 1 out of a hundred patients taking an ARB other than olmesartan were hospitalized with a discharge diagnosis of celiac disease, 4.82 olmesartan users would be hospitalized with a discharge diagnosis of celiac disease.
Q. A fourfold increase according to these data?
A. Almost five.
Q. Almost five.
Doctor, in terms of the number of files examined, how does this study compare with the Mini-Sentinel?
A. The number of patient years examined, you're asking?
Q. Patient years or files out of which the analysis in the Mini-Sentinel was done -- let me back up.

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Do you know how the Mini-Sentinel was done?
A. I wouldn't say I know exactly how it's done, no.
Q. So you can't compare the size of the database that the FDA was looking at to arrive at their conclusions compared to what the French folks were looking at.
A. I was not going to make that comparison, no.
Q. Okay.
Isn't the result obtained for celiac disease by the French people looking at their French data for olmesartan compared to other ARBs inconsistent with the FDA's analysis in the Mini-Sentinel on celiac disease?
MR. SLATER: Objection; foundation.
(Pause.)
THE WITNESS: I don't see the Mini-Sentinel here. I don't know.

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MR. PARKER: Okay. Fair enough.
BY MR. PARKER:
Q. Doctor, I want to change subjects in the time I have left and move around a little bit.
A. Sure.
Q. Do you have an understanding of what is meant by the Bradford Hill criteria?
A. I do.
Q. Those criteria are not addressed, not mentioned, in your report; correct?
A. Not specifically, no.
Q. Have you ever published a paper of any type in which you used the Bradford Hill criteria to arrive at a conclusion of whether cause and effect relationship existed between a drug and an outcome?
A. I think that the Bradford Hill criteria is something that we learn about in medicine and think about when

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we're evaluating those questions, but I've never -- I've never, you know, specifically written a paper in which I looked at each point and made a response.
Q. I take it from your last answer that in the period of time that you were writing your general causation report, you were aware of and understood the Bradford Hill factors criteria.
A. I was familiar with the criteria.
Q. And what is their use in medical science?
A. They are a set of questions which are used to address cause and effect.
Q. Can you explain for me why that methodology was not used in your report?
A. I think it influences my thinking, those points influence my thinking. I didn't explicitly go through them because -- I don't know. Just did not do that.